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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application for Reissue of: Patent No. 5,443,833		§	
Patentee:	ANDREW R. CLARK PAUL WRIGHT JULIA H. RATCLIFFE	§ § §	Attorney Docket No.: 2553.004
Issued:	August 22, 1995	§	
For:	PHARMACEUTICAL COMPOSITIONS	§ §	

REISSUE APPLICATION TRANSMITTAL LETTER

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Enclosed for filing please find the Reissue Application papers of ANDREW R. CLARK PAUL WRIGHT for Pharmaceutical Compositions.

This application is a reissue of U.S. Patent No. 5,443,833 issued on August 22, 1995 to the above named inventors. The following documents are also enclosed:

1. Reissue Declaration of Andrew Clark pursuant to 37 C.F.R. § 1.63 and 1.175(a);
2. Unexecuted Reissue Declaration of Paul Wright pursuant to 37 C.F.R. § 1.63 and 1.175(a);
3. Power of Attorney;
4. Offer to Surrender;
5. Order for Title Report;
6. Postcard Receipt;
7. Corroborating Declarations pursuant to 37 C.F.R. § 1.175(b) of Alison Blakey, Stephen Jones and James Napoli;
8. Assent of Assignee to Reissue;
9. Proposed Reissue Claims;
10. Copy of U.S. Patent 5,443,833 which has 12 pages of specifications (including abstract and detailed description of the invention) and three claims; and

11. Petition for Filing Reissue Application by other than all of the Inventors, including supporting declarations of Andrew Agnew and John T. Polasek;
12. Copy of Certificate of Correction dated April 2, 1996.

A check in the amount of $1085.00 is enclosed; $930.00 for the filing fee, $25.00 for the Title Report, and $130.00 for the Petition for Filing Reissue Application by Other Than All the Inventors.

If for any reason the check is missing or insufficient, the Commissioner is authorized to charge any additional fees which may be required (or credit any overpayment) to Deposit Account No. 20-1299; Order No. 2553.004/EWG.

If any additional informalities are identified by the Examiner, please contact the undersigned attorney at (713) 877-1515.

Respectfully submitted,

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Approved for use through 05/31/96. OMB 0651-0033
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE<

REISSUE APPLICATION FEE DETERMINATION RECORD	Docket Number (Optional) 2553.004 EWG

Claims as Filed - Part 1

Claims in Patent	For	Number Filed in Reissue Application	(3) Number Extra	Small Entity Rate	Small Entity Fee		Other than a Small Entity Rate	Other than a Small Entity Fee
(A) 3	Total Claims (37 CFR 1.16(i))	(B) 13	**** 0 =	x $__ =		or	x $80 =	0
(C) 3	Independent Claims (37 CFR 1.16(i))	(D) 5	* 2 =	x $__ =			x $80 =	160
				Basic Fee (37 CFR 1.16(h))	$ 0			$770.
				Total Filing Fee	$ 0.	OR		$ 930.

Claims as Amended - Part 2

	(1) Claims Remaining After Amendment		(2) Highest Number Previously Paid For	(3) Extra Claims Present	Small Entity Rate	Small Entity Fee		Other than a Small Entity Rate	Other than a Small Entity Fee
Total Claims (37 CFR 1.16(j))	***	MINUS	**	* =	x $__ =		or	x $__ =	
Independent Claims (37 CFR 1.16(i))	***	MINUS	*****	=	x $__ =			x $__ =	
				Total Additional Fee	$		OR		$

* If the entry in (D) is less than the entry in (C), Write "0" in column 3.
** If the "Highest Number of Total Claims Previously Paid For" is less than 20, Write "20" in this space.
*** After any cancelation of claims
**** If "A" is greater than 20, use (B -A); if "A" is 20 or less, use (B - 20).
***** "Highest Number of Independent Claims Previously Paid For" or Number of Independent Claims in Patent (C).

☐ Please charge Deposit Account No. _____ in the amount of _____.
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☒ A check in the amount of $ 1085.00 to cover the filing / additional fee is enclosed.

8/21/97
Date

Signature of Applicant, Attorney or Agent of Record

Edward W. Goldstein
Typed or printed name

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United States Patent [19]

Clark et al.

[54] PHARMACEUTICAL COMPOSITIONS

[75] Inventors: Andrew R. Clark, Loughborough; Paul Wright, Bramcote; Julia H. Ratcliffe, Gosport, all of England

[73] Assignee: Fisons plc, Ipswich, England

[21] Appl. No.: 82,804

[22] Filed: Jun. 25, 1993

Related U.S. Application Data

[63] Continuation of Ser. No. 742,574, Aug. 7, 1991, abandoned, which is a continuation of Ser. No. 410,020, Sep. 20, 1989, abandoned, which is a continuation of Ser. No. 133,520, Dec. 16, 1987, abandoned.

[30] **Foreign Application Priority Data**

Dec. 23, 1986	[GB]	United Kingdom	8630767
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Dec. 24, 1986	[GB]	United Kingdom	8630904
Mar. 20, 1987	[GB]	United Kingdom	8706684

[51] Int. Cl.[6] A61K 9/00

[52] U.S. Cl. 424/400; 424/489; 424/434

[58] Field of Search 424/489, 400, 450, 434; 546/97

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,328,341	5/1982	Raphael	546/92
4,419,352	12/1983	Cox	424/248.4
4,474,787	10/1984	Cairns	424/258
4,698,345	10/1987	Dicker	514/291
4,760,072	7/1988	Brown	514/291
4,849,427	7/1989	Nassim	514/291
4,866,072	9/1989	Edwards	514/291
4,868,192	9/1989	Totton	514/291

FOREIGN PATENT DOCUMENTS

0004722	1/1983	Japan .
2022078	12/1979	United Kingdom .
2157291A	4/1985	United Kingdom .

OTHER PUBLICATIONS

Patel, K. R. "Dose-Response Study of Sodium Cromoglycate in Exercise-Induced Asthma," *Thorax*, vol. 37, pp. 663-666.

US005443833A

[11] Patent Number: 5,443,833

[45] Date of Patent: Aug. 22, 1995

Br. J. Clin. Pharmac., vol. 24, Oct. 1987, pp. 493–501, "The Pharmacokinetics of Nedocromil Sodium, a New Drug for the Treatment of Reversible Obstructive Airways Disease, in Human Volunteers and Patients With Reversible Obstructive Airways Disease".

J. Med. Chem., vol. 28, No. 12, 1985, pp. 1832–1842, American Chemical Society, H. Cairns et al., "New Antiallergic Pyrano(3,2-g)quinoline-2,8-dicarboxylic Acids with Potential for the Topical Treatment of Asthma".

P. H. List: "Arzneiformenlehre" Chapter Konservierungmittel pp. 369–373, 1976.

P. H. List: "Arzneiformenlehre" Chapter Augenarzneien pp. 400–410, 1976.

R. Voigt: "Lehrbuch der pharmazeutischen Technologie", Chapter 27 Augentropfen, pp. 459–467, 1975.

Eur. J. Respir. Dis. (Suppl. 147) 1986, pp. 120–131, R. M. Auty: "The clinical development of a new agent for the treatment of airway inflammation, nedocromil sodium (Tilade)".

(List continued on next page.)

Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Marshall, O'Toole, Gerstein, Murray & Borun

[57] ABSTRACT

A method of treatment of a condition selected from the group comprising conjunctivitis, keratitis, 'allergic eyes', adenovirus infections, corneal homograft rejection, anterior uveitis, nasal polyps, vasomotor rhinitis, allergic manifestations of the nasopharynx, reversible obstructive airways disease, Crohn's disease, distal colitis and proctitis, which method comprises administration to a patient suffering from such a condition of a therapeutically effective amount of an aqueous solution containing, as active ingredient, 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrano(3,2-g)quinoline-2,8-dicarboxylic acid or a pharmaceutically acceptable salt thereof. Also described are novel pharmaceutical compositions suitable for use in such methods of treatment.

3 Claims, No Drawings

OTHER PUBLICATIONS

J. Allergy Clin. Immunol. vol. 79, No. 1, Feb. 19–25, 1987, p. 186, abstract 247. Schwartz et al. "Efficacy of hedocromil sodium . . . ragweed seasonal allergic rhimitis (SAR)".

J. Allergy Clin. Immuno. vol. 80, No. 2, Aug. 1987, pp. 218–222, Corrado et al. "The effect of nedocromil sodium on nasal provocation with allergen".

J. Allergy Clin. Immunol., vol. 81, No. 3, Mar. 1988, pp. 570–574 Ruhno et al. "Intranasal nedocromil sodium in the treatment of ragweed-allergic rhinitis".

Invest. Ophtalmol. Visual Sci., vol. 29, May 1–6, 1988.

p. 229, Stockwell et al. "Dougle blind group comparative trial of 2% nedocromil . . . seasonal allergic conjunctivitis".
Pharmazie, vol. 37, No. 4, 1982, pp. 261–263 Pohloudek–Fabini et al. "Zur Stabilitat der Phenylquecksilbersalze".
Journal of Pharmaceutical Sciences, vol. 65, No. 4, Apr. 1976, pp. 628–630, Grady et al. "Testing of heat sealing by thermal analysis".
R. Voight, "Lehrbuch der pharmazeutischen Technologie," 5th edition, 1984, pp. 554–557, Verlag Chemie, Weinheim, DE.

PHARMACEUTICAL COMPOSITIONS

This is a Continuation of U.S. application Ser. No. 07/742,574, filed Aug. 7, 1991, now abandoned; in turn a Continuation of Ser. No. 07/410,020 filed Sep. 20, 1989, now abandoned; in turn a Continuation of Ser. No. 07/133,520 filed Dec. 16, 1987, now abandoned.

FIELD OF THE INVENTION

This invention relates to methods of treatment and to novel pharmaceutical compositions for use in such methods.

DESCRIPTION OF THE PRIOR ARTS

In British Patent No 2022078 there are disclosed a number of pyranoquinoline compounds which are indicated for use in the treatment of reversible airway obstruction. Pharmaceutical compositions containing these compounds are also described, especially compositions in which the active ingredient is in powder form with a mass median diameter of from 0.1 to 10 microns. British Patent Application No 2157291A describes the particular utility of the disodium salt of one of these compounds, 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrano(3,2-g)quinoline-2,8-dicarboxylic acid, in the treatment of reversible airway obstruction. Also described are powdered aerosol compositions of this salt for administration to the lung and physical forms of the salt which are especially suitable for formulation in this way.

BRIEF SUMMARY OF THE INVENTION

We have now surprisingly found that when it is administered in aqueous solution the same compound is efficacious in the treatment of a variety of disorders of the eye, notably conjunctivitis, as well as in the treatment of certain disorders associated with other organs.

Thus, according to the invention there is provided a method of treatment of a condition selected from the group comprising:

- conjunctivitis, keratitis, 'allergic eyes', adenovirus infections, corneal homograft rejection, anterior uveitis;
- nasal polyps, vasomotor rhinitis, allergic manifestations of the nasopharynx;
- reversible obstructive airways disease;
- Crohn's disease, distal colitis and proctitis, which method comprises administration to a patient suffering from such a condition of a therapeutically effective amount of an aqueous solution of 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrano(3,2-g)quinoline-2,8-dicarboxylic acid or a pharmaceutically acceptable salt thereof.

By the term 'conjunctivitis' we mean inflammatory disorders of the conjunctiva commonly characterised by photophobia and irritation. The condition may be bacterial or vital and encompasses a number of specific types of conjunctivitis; for instance, seasonal allergic conjunctivitis, perennial allergic conjunctivitis, vernal catarrh (vernal kerato-conjunctivitis), 'irritable eye' or 'non-specific conjunctivitis', Herpes Simplex Conjunctivitis, Herpes Zoster Conjunctivitis and phlyctenular conjunctivitis.

Similarly, by the term 'keratitis' we mean inflammation of the cornea which may involve its superficial surface ('superficial keratitis' including the localised form known as 'corneal ulceration') or be confined to

the deeper layers ('interstitial keratitis'). Other particular forms of keratitis which may be mentioned include Herpes Simplex Keratitis and Herpes Zoster Keratitis.

Proctitis includes chronic (ie ulcerative) and non-specific proctitis.

DETAILED DESCRIPTION OF THE INVENTION

Pharmaceutically acceptable salts of the active ingredient include salts with metal cations, such as alkali metal cations. We particularly prefer the disodium salt which is commonly referred to as nedocromil sodium.

The solution is administered by a route appropriate to the condition being treated. For instance, administration may be to the eye, intra-nasally (e.g. as a nasal spray), by inhalation as a nebulised cloud or rectally as an enema.

We prefer administration of the solution to be by a route other than by inhalation. In particular, we prefer administration to be to the eye.

The solution may contain from about 0.1 to 10% w/v of the active ingredient. However, we prefer the active ingredient to be present at a level of less than 5% and more particularly less than 3% w/v, e.g. 0.5%, 1.0% or 2.0% w/v. The concentration of choice will depend of course inter alia on the nature of the condition to be treated, its severity and the mode of administration of the solution.

In addition to the active ingredient the solution generally contains one or more pharmaceutically acceptable additives. Examples of classes of additive which may be present are:

a) chelating or sequestering agents,

b) preservatives, and

c) viscosity-modifying agents.

Suitable chelating or sequestering agents include sodium carboxymethyl cellulose, citric, tartaric or phosphoric acid, and amino carboxylate compounds. The preferred chelating agent, however, is ethylenediamine tetraacetic acid or a salt thereof, especially its di-sodium salt.

The concentration of the chelating or sequestering agent should be such as to ensure that no precipitate of metal salts of the active ingredient occurs. A suitable concentration of chelating or sequestering agent may be from 0.005 to 0.5, e.g. 0.01 or 0.1% w/v.

The choice of preservative, where the solution contains a preservative, may depend on the route of administration. Preservatives suitable for solutions to be administered by one route may possess detrimental properties which preclude their administration by another route. For nasal and ophthalmic solutions, preferred preservatives include quaternary ammonium compounds, in particular the mixture of alkyl benzyl dimethyl ammonium compounds known generically as 'Benzalkonium Chloride'. For solutions to be administered by inhalation, however, the preferred preservative is chlorbutol. Other preservatives which may be used, especially for solutions to be administered rectally, include alkyl esters of p-hydroxybenzoic acid and mixtures thereof, such as the mixture of the methyl, ethyl, propyl and butyl esters which is sold under the tradename "Nipastat".

The concentration of preservative should be such as to ensure effective preservation of the solution ie such that bacterial growth in the solution is inhibited. For most preservatives the concentration will typically lie in the range 0.001 to 0.1% w/v. However, in the case of

chlorbutol acceptable concentrations are greater than 0.25% but less than 0.6% w/w ie the concentration of chlorbutol is 0.25 to 0.6%, preferably 0.3 to 0.55% e.g. 0.5% w/w.

Suitable viscosity enhancing agents which may be incorporated into the solution include carbomers ie polymers of acrylic acid cross-linked with a polyalkenyl polyether, ~~aluminium~~ magnesium silicate, methylcellulose, hydroxypropyl methylcellulose and other cellulose derivatives.

The viscosity of the solution will depend, inter alia, on the particular viscosity enhancing agent used and its molecular weight and on the target organ. However, the solution preferably has a viscosity of at least 100 cps, more preferably at least 200 cps and especially more than 400 cps, at a shear rate of 50 s^{-1}. The viscosity of the solution is preferably less than 10000 cps, more preferably less than 1000 cps and especially less than 500 cps, at a shear rate of 50 s^{-1}.

Viscosities are preferably determined using a rotational viscometer such as a Rheomat 30 (Rheomat is a Trade Mark), at a temperature of from 15° to 25° C. e.g. 20° C.

For applications which involve the solution being administered as a spray e.g. through a nasal pump, we prefer the viscosity enhancing agent to have a low viscosity at high shear rates, e.g. from about 100 cps to about 300 cps at 140 s^{-1}, and a high viscosity at low shear rates, e.g. from about 700 cps to about 1200 cps at 15 s^{-1}.

Viscosity enhancing agents which we prefer include hydroxypropyl methylcellulose and carbomers, in particular the carbomer sold as Carbopol 934, the viscosity of a neutralised 0.5% w/w aqueous dispersion of which lies in the range 29400 to 39400 cps and the heavy metal content of which is 0.002% or less. ~~10~~ The amount of viscosity-modifying agent required to achieve the desired viscosity will depend on the particular agent used and also on its molecular weight. However, we prefer to use up to about 2% w/w, e.g. 0.5 to 1.5% w/w of viscosity enhancing agent.

The solution may also contain other conventional excipients, e.g. sodium chloride, dextrose or mannitol, and buffers, e.g. sodium dihydrogen orthophosphate (sodium acid phosphate BP), di-sodium hydrogen phosphate (sodium phosphate BP) sodium citrate/citric acid, and boric acid/sodium borate. The proportion and concentration of excipients and buffers may be varied within fairly wide ranges, provided the resulting solution is stable and non-irritant when applied to the appropriate tissues. The maximum total concentration of excipients and buffers is preferably less than 5% w/v and more preferably less than 2% w/v. Solutions for rectal administration may contain bulking agents, e.g. methyl cellulose, to aid retention in the bowel.

The solution may be made isotonic with physiological fluids by the incorporation of a suitable tonicity agent e.g. sodium chloride. The solution typically contains from about 0.1 to 1.0, more typically 0.5 to 1.0% w/v sodium chloride.

Although physiological pH is about 7.4, we prefer the pH of the solution to be in the range 3.5 to 6, preferably 4 to 5.5. In this range of pH, the stability of the solution is enhanced, surprisingly with no deleterious effects such as undue tissue irritation.

The composition of the invention may be made up, for example, by dissolving the active ingredient, chelating or sequestering agent (if included) and excipients (if

included) in freshly distilled water, adding to this solution an aqueous solution containing the preservative (if included), adjusting the pH if necessary, making the solution up to the desired volume with distilled water, stirring and then sterilising. Alternatively, the active ingredient, chelating or sequestering agent (if included) and excipients (if included) may be dissolved in a solution containing the preservative. Sterilisation is preferably performed by sterile filtration into a previously sterilised container. Where the preservative used is benzalkonium chloride, some complex formation may occur when the solutions of active ingredient and preservative are mixed. It may thus be necessary to use a higher concentration of preservative than is desired for the final product.

Aqueous solutions containing active ingredient, a viscosity enhancing agent, e.g. a carbomer, and, optionally, a preservative, e.g. benzalkonium chloride, may be prepared by dispersing the viscosity enhancing agent in an aqueous solution containing the preservative (if used) and the active ingredient, and then, if required, adjusting the pH, e.g. by addition of sodium hydroxide, and, if desired, further diluting the solution with water.

The solution of the preservative and the active ingredient may be made simply by dissolving the ingredients in water which is low in metal ions.

The solution is preferably made up at a temperature of from about 10° to 50° C., for example at room temperature.

The solution may be put up in unit dosage form, in which case preservatives may be incorporated, but are generally not necessary. Alternatively the solution may be put up in multi-dose form. In general it will be necessary to incorporate one or more preservatives into multi-dose solutions to ensure that the solution remains sterile after initial use.

Conventionally, unit doses of aqueous solutions for use in nebulisers are packed in glass or plastics ampoules which are broken open immediately prior to use. Such packaging is both wasteful and expensive to manufacture. Furthermore, the breaking-open of glass ampoules could lead to the formation of glass sherds which can be inhaled with the solution.

We have now found a form of packaging for single-dose solutions which overcomes the above-mentioned disadvantages. Thus, according to a further aspect of the invention, we provide a soft ampoule of plastics material sterile-filled with a unit dose of an aqueous solution containing, as active ingredient, 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrano(3,2-g)quinoline-2,8-dicarboxylic acid or a pharmaceutically acceptable salt thereof, and sealed.

We prefer the plastics material to be permeable to carbon dioxide. Thus, when the ampoule is stored, carbon dioxide dissolves in the solution and the pH is lowered. Since the stability of the active ingredient is greater at lower pH, this has the effect of enhancing the stability of the solution.

Suitable plastics materials from which the ampoule may be manufactured include low-density polyethylene.

A plurality of ampoules may be connected to, and formed integrally with, an anchorage member which may be adapted to receive a label or writing, e.g. to identify the contents of the ampoules.

The plastics material may include a pigment or pigments such that the ampoules correspond in colour to the solution contained within them.

Multi-dose solutions may be packaged in volumes of 5 to 300 ml. Preferred volumes for inhalation compositions include 60, 120 and 240 ml. For nasal and ophthalmic compositions multi-dose packs preferably contain from 5 to 20 ml of solution.

We prefer multi-dose solutions to be packaged such that unit volumes of the solution to be administered can be accurately dispensed. The solution may, for example, be packaged in a flexible-walled container provided with a cap to receive the unit volume.

The dosage to be administered will of course vary with the condition to be treated, with its severity and with its location. However, in general for use in the eye a dosage of about 1 or 2 drops (e.g. from about 0.3 to 1.2 mg of active ingredient depending on the concentration of active ingredient) into the affected eye from 2 to 4 times a day is found to be satisfactory. More frequent dosage may, of course, be used if desired. For use in the nose a dosage of about 0.25 ml (e.g. from about 1.2 mg to 5.0 mg of active ingredient) is indicated.

For rectal administration a total daily dosage of from about 50 to 1000 mg of active ingredient, more preferably 100 to 400 mg, administered in smaller doses 2 to 4 times a day is found to be satisfactory. A dosage unit may conveniently contain from about 25 to 200 mg of active ingredient.

For administration by inhalation a daily dosage of from about 10 mg to 100 mg is, in general, found to be satisfactory. The daily dosage may be administered in divided doses, e.g. from 2 to 4 times a day. More frequent dosage may of course be used if required.

The aqueous solutions according to the present invention are advantageous in that they are longer acting, more acceptable to the patient, give rise to higher concentrations of active ingredient in target tissues, give rise to effective concentrations of active ingredient in target tissues for a longer time or are more stable than known similar formulations.

The invention is illustrated, but in no way limited, by the following Examples.

Example 1

Non-preserved nebuliser solution

Nedocromil Sodium	0.5% w/v
Sodium Chloride	0.79
Hydrochloric acid	q.s.
Purified Water	to 100

Nedocromil sodium (5 g) and sodium chloride (7.9 g) were dissolved in purified water (900 ml). The pH of the solution was adjusted to between 5 and 5.5 by addition of hydrochloric acid and the volume made up to 1000 ml with purified water.

The solution was sterile-filled into low-density polyethylene ampoules which were then sealed.

Example 2

Preserved nebuliser solution

Nedocromil Sodium	0.5% w/v
Sodium Chloride	0.79
Chlorbutol	0.5
Sodium hydroxide	q.s.
Purified Water	to 100

Chlorbutol (5 g) was dissolved in purified water (900 ml). Nedocromil sodium (5 g) and sodium chloride (7.9

g) were then added to the solution. The pH of the solution was adjusted to between 5 and 5.5 by addition of sodium hydroxide and the volume made up to 1000 ml with purified water.

The solution was filled into polyethylene bottles of 120 ml capacity.

Example 3

Nasal Solution

Nedocromil Sodium	1.00% w/v
Sodium Chloride	0.715
Disodium Edetate	0.01
Benzalkonium Chloride	0.02
Purified Water	to 100

Nedocromil sodium (100 g), sodium chloride (71.5 g) and disodium edetate (1 g) were dissolved in approximately 5 liters of purified water. To this solution a dispersion of benzalkonium chloride solution 50% USNF (4 g) in approximately 1 liter of purified water was added. The solution was made up to 10 liters with purified water, stirred for 30 minutes, filtered to remove any complex formed and then sterile filtered and filled into bottles.

Example 4

Opthalmic Solution

Nedocromil Sodium	2.00% w/v
Benzalkonium Chloride	0.01
Disodium Edetate	0.05
Sodium Chloride	0.55
Purified Water	to 100

Prepared by the method of Example 3 above.

Example 5

Viscous Nasal or Ophthalmic Solution

Nedocromil sodium	1.0% w/w
Disodium edetate	0.1
Benzalkonium chloride	0.01
Carbopol 934P	0.75
Sodium hydroxide	q.s.
Purified water	to 100

20 g of nedocromil sodium and 2 g of disodium edetate were dissolved in approximately 600 g of purified water. A dispersion of 0.808 g of Benzalkonium Chloride Solution 50% USNF in approximately 200 g of purified water was added and the resulting dispersion made up to 1000 g with purified water and stirred for 30 minutes.

The dispersion was filtered through a glass fibre prefilter and the first 100 ml discarded. The remainder of the filtered solution was filtered through a pre-sterilised 0.22 um membrane filter and the filtrate collected.

250 g of the filtrate was added to 4.15 g of Carbopol 934P and stirred until the Carbopol was fully dispersed. The pH of the dispersion was adjusted to between pH 5.5 and 5.8 by addition of 2M sodium hydroxide solution. The dispersion was mixed until a homogeneous uniform gel was formed. The gel was made up to 500 g with purified water, remixed and filtered through a 13 um stainless steel filter.

The viscosity of the solution at 20° C. and a shear rate of $50s^{-1}$ was found to lie in the range 420–480 cps.

Example 6

Enema Solution

Nedocromil Sodium	0.15% w/v
Nipastat (Nipastat is a trademark)	0.10
Sodium Chloride	0.812
Purified Water	to 100

Methyl cellulose or other agents may be added to aid retention of the solution in the bowel.

Example 7

Study of 2% Nedocromil Sodium Eye-Drops in the Treatment of Seasonal Allergic Conjunctivitis

32 patients (11 male, 21 female) with ages in the range 4 to 69 (average 25.2) participated in an investigation of the efficacy of an aqueous solution of nedocromil sodium in the treatment of seasonal allergic conjunctivitis. The solution used had the composition given in Example 4. One drop (0.04 ml) was administered per eye four times a day for four weeks.

At the end of the trial, both the patient and the supervising clinician were asked to rate the effectiveness of the treatment, using the following 0–3 scale:

0=no control of symptoms
1=slight control
2=moderate control
3=full control

In addition the patients were asked whether the eye-drops were an acceptable form of treatment.

For the 23 patients who completed the trial, the results were as follows:

Rating	No of patients	
	Patients' assessment	Clinicians' assessment
3	10	7
2	9	9
1	2	4
0	1	1

(One patient failed to record an opinion, and the clinician failed to record an opinion for two patients).

18 of the 23 patients recorded that they found the treatment acceptable.

We claim:

1. A method of treating a reversible obstructive airways disease comprising administering, by inhalation, to a patient suffering from, or susceptible to, such a condition the nebulized contents of an ampoule of carbon dioxide permeable plastics material filled with a unit dose of an aqueous pharmaceutical solution containing, as active ingredient, from 0.1 to 5% w/v of 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrano(3,2-g)quinoline-2,8-dicarboxylic acid or a pharmaceutically acceptable salt thereof, the solution having a pH of 3.5 to 6.0.

2. The method of treatment according to claim 1, wherein the concentration of the active ingredient in the solution is from 0.1 to 1.0% w/v.

3. The method of treatment according to claim 1, wherein the active ingredient is nedocromil sodium.

* * * * *

We claim:

4. A method of treatment of a disease selected from the group consisting of conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, which method comprises administering to the eye an effective amount of an ophthalmically acceptable aqueous pharmaceutical solution containing an active ingredient 9-ethyl-6, -dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8-dicarboxylic acid, or a pharmaceutically acceptable salt thereof.

5. The method of claim 4, wherein the disease is conjunctivitis.

6. The method of claim 5, wherein the disease is seasonal allergic conjunctivitis.

7. The method of claim 5, wherein the disease is allergic conjunctivitis.

8. The method of claim 5, wherein the disease is vernal conjunctivitis.

9 The method of claims 4, 5, 6, 7 or 8, wherein said active ingredient is nedocromil sodium.

10. A method of controlling the symptoms of conjunctivitis comprising administering to the eye of a patient having conjunctivitis an effective amount of nedocromil sodium in an ophthalmically acceptable formulation.

11. The method of claim 10, wherein the conjunctivitis is vernal conjunctivitis.

12. The method of claim 10, wherein the conjunctivitis is allergic conjunctivitis.

13. The method of claim 10, wherein the conjunctivitis is seasonal allergic conjunctivitis.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application for Reissue of: Patent No. 5,443,833		§	
Patentees:	ANDREW R. CLARK PAUL WRIGHT JULIA H. RATCLIFFE	§ § §	Attorney Docket No.: 2553.004
Assignee:	Fisons, plc	§	
Issued:	August 22, 1995	§	
For:	PHARMACEUTICAL COMPOSITIONS	§	

REISSUE DECLARATION OF ANDREW CLARK UNDER 37 C.F.R. 1.63 AND 1.175(a)

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

As a below-named inventor, I hereby declare:

1. My residence, post office address, and citizenship are as stated below, underneath my name.

2. I verily believe Andrew R. Clark, Paul Wright, and Julia H. Ratcliffe to be the original, first, and joint inventors of the subject matter which is claimed in original Letters Patent No. 5,443,833 granted August 22, 1995, based upon Application Serial No. 08/082,804 filed June 25, 1993 as a continuation of Application Serial No. 07/742,574 filed August 7, 1991, now abandoned, which is a continuation of Application Serial No. 07/410,020 filed September 20, 1989,

now abandoned, which is a continuation of Application Serial No. 07/133,520 filed December 16, 1987, now abandoned, and Andrew R. Clark, Paul Wright, and Julia H. Ratcliffe to be the original, first, and joint inventors of the subject matter of the invention claimed in this application for a reissue patent being filed concurrently herewith.

3. As set forth in my original Declaration for Patent Application, I claim foreign priority benefits under Title 35 United States Code, § 119 of the following foreign applications for patent or inventors certificate and have also identified below any foreign application for patent or inventors certificate having a filing date before that of the application on which priority is claimed:

Great Britain - 86/30767, filed December 23, 1986 - Priority claimed
Great Britain - 86/30769, filed December 23, 1986 - Priority claimed
Great Britain - 86/30904, filed December 24, 1986 - Priority claimed
Great Britain - 87/06684, filed March 20, 1987 - Priority claimed

4. At the time US Application Serial No. 07/133,520 was filed, I was an employee of Fisons, plc, of Ipswich England. In 1992, I left the employ of Fisons plc. I do not have any information concerning the current whereabouts of Julia Ratcliffe. However, upon information and belief, and as evidenced by the Declaration for Patent Application filed with the original application, Julia Ratcliffe is a citizen of Great Britain and she used to reside at Flat 2, 16 Crescent Road, Alverstoke, Gosport Hampshire, England, her last known address.

5. I have reviewed and understood the contents of the specification, including the claims, of this reissue application.

6. I do not know and do not believe that said invention was ever known or used in the United States before my invention thereof.

7. I verily believe the original patent to be wholly or partly inoperative or invalid by reason of claiming less than I had a right to claim in the patent because claims for the use of the aqueous pharmaceutical solution of original claims 1-3 in the method of treating ophthalmic conditions and controlling the symptoms of ophthalmic conditions were erroneously canceled. When I filed my original application the intended utilities of the claimed aqueous pharmaceutical solution containing as active ingredient, 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof, included methods of treating a disease or condition selected from the group consisting of conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, which comprises administering to the eye an effective amount of an ophthalmically acceptable aqueous pharmaceutical solution; and methods of controlling the symptoms of conjunctivitis comprising administering to the eye of a patient having conjunctivitis an effective amount of nedocromil sodium in an ophthalmically acceptable formulation. This is illustrated in the body of the original patent, for example col. 1, lines 34-44. In fact, upon information and belief, claims related to a method of treating ophthalmic conditions and those symptoms, were included throughout much of the prosecution of the above referenced applications. Original claims 1-3, the only claims in this patent, do not claim these utilities. I do not have personal knowledge why the aspect of the claims related to the method of treating ophthalmic conditions was canceled. Further I was not consulted when this aspect of the claims was canceled. In fact, I do not recall having any substantive involvement in the prosecution of the applications leading to the issuance of the original patent after I left the employ of Fisons plc.

8. Upon information and belief, this error arose because the Fisons attorney in charge of handling the prosecution of my application failed to continue prosecution of claims directed at

methods of treating ophthalmic diseases and conditions after the examiner had allowed claims directed at treating reversible obstructive airways disease. Upon information and belief, in the original application, and during the prosecution of Application Serial No. 08/082,804, claims reciting methods of treating various types of conditions, including ophthalmic conditions were submitted. Upon information and belief, the Examiner's remarks in the Final Office Action of Application Serial No. 08/082,804 were directed to the formulation of the aqueous pharmaceutical solution claimed in the invention in the treatment of reversible obstructive airways disease. However, upon information and belief, all of the pending claims in the application were canceled in an Amendment after the final rejection filed February 13, 1995, including those for methods of treating and controlling the symptoms of ophthalmic conditions, and three new claims unnecessarily limited to methods of treating reversible obstructive airways disease were submitted. These three new claims issued as claims 1-3 in U.S. Patent No. 5,443,833 on August 22, 1995.

9. Upon information and belief, this error occurred due to a failure of the Fisons attorneys to continue prosecution of claims for methods of treating and controlling symptoms of ophthalmic conditions. At the time the error occurred, I was not involved in decisions relating to the prosecution of the application and therefore, all actions relating to the prosecution was made by the Fisons' attorneys. Upon information and belief, the failure to continue prosecution of claims directed at a method for treating ophthalmic conditions may have been the result of internal turmoil within Fisons plc. Upon information and belief, during 1995, Fisons plc was acquired by Rhone-Poulenc Rorer, Inc. and a number of Fisons employees left the company in this time frame. As explained above, I left the employ of Fisons before the amendment was made. I am informed that the declaration of Alison Blakey is being submitted to more fully explain the error.

10. This error that rendered this patent wholly or partly inoperative arose entirely from inadvertence, accident, and mistake, and without any fraudulent and/or deceptive intent on my part, or, on my best information and belief, without any fraudulent and/or deceptive intent on the part of Paul Wright, Julia Ratcliffe or anyone else associated with me.

11. As a result of the Fison's attorneys' erroneous conclusion or decision, the patent is wholly or partly inoperative or invalid by reason of claiming less than I had a right to claim in the patent because original claims 1-3 do not recite the use of the aqueous pharmaceutical solution of original claims 1-3 for use in methods of treating ophthalmic conditions and controlling the symptoms of ophthalmic conditions.

12. Upon information and belief this error was discovered in 1997, during license negotiations for the use of the aqueous pharmaceutical solution claimed in original claims 1-3 for methods of treating ophthalmic diseases and controlling the symptoms of ophthalmic conditions. Upon information and belief, a review of the specification of this patent by the potential licensee revealed support for claims for methods of treating and controlling the symptoms of ophthalmic conditions. Upon information and belief, the potential licensee then reviewed the file history and the prior art cited and relied upon by the Examiner during the prosecution of U.S. Patent No. 5,443,833, and concluded that the claims for methods of treating and controlling symptoms of ophthalmic conditions were patentable. Of course this is consistent with my belief that the subject matter was new and therefore patentable. In fact, as evidence that an error did in fact occur, upon information and belief, all relevant prior art was cited to the European Patent Office and successfully overcome to establish patentability of claims for methods of treating reversible obstructive airways disease, as well as for methods of treating and controlling the symptoms of ophthalmic conditions.

13. The error of canceling claims which recite the use of the aqueous pharmaceutical solution containing as active ingredient, 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof, as claimed in original claims 1-3, which included methods of treating and controlling the symptoms of ophthalmic conditions is remedied in this reissue application because reissue claims 4-13 recite the use of the aqueous pharmaceutical solution of original claims 1-3 for use in the methods of treating and controlling the symptoms of ophthalmic conditions. Therefore, there is a difference in the scope of the claims 1-3 of U.S. 5,443,833 and the reissue claims. The following identifies all of the reissue claims presently in this application and the differences, if any, between the reissue claims and original claims 1-3:

a. Reissue claims 1-3 are identical to original claims 1-3 issued in this patent.

b. Reissue claim 1 recites the method of treating reversible obstructive airways disease comprising administering, by inhalation, to a patent suffering from, or susceptible to, such a condition the nebulized contents of an ampoule of carbon dioxide permeable plastics material filled with a unit dose of an aqueous pharmaceutical solution containing, as active ingredient, from 0.1 to 5% w/v of 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof, the solution having a pH of 3.5 to 6.0. Reissue claim 1 is identical to original claim 1.

c. Reissue claim 2 is dependent on reissue claim 1 with the further limitation that the concentration of the active ingredients in the solution is from 0.1 to 1.0% w/v. Reissue claim 2 is identical to original claim 2.

d. Reissue claim 3 is dependent on reissue claim 1 with the added limitation that the active ingredient is nedocromil sodium. Reissue claim 3 is identical to original claim 3.

e. Reissue claim 4 is an independent claim which recites the method of treatment for a disease selected from the group consisting of conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, which comprises administering to the eye an effective amount of an ophthalmically acceptable aqueous pharmaceutical solution containing an active ingredient 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof. Reissue claim 4 differs from original claims 1-3 because reissue claim 4 recites the use of an ophthalmically acceptable aqueous solution of pharmaceutical solution containing an active ingredient of 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof in the method of treating a disease selected from the group consisting of conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, a utility not claimed in original claims 1-3. Reissue claim 4 also differs from original claims 1-3 because reissue claim 4 recites administering to the eye an effective amount of an ophthalmically acceptable aqueous pharmaceutical solution. Reissue claim 4 does not recite administering the pharmaceutical solution by inhalation, the nebulized contents of an ampoule of carbon dioxide permeable plastics material filled with a unit dose of the aqueous pharmaceutical solution. Further, reissue claim 4 differs from original claims 1-3 because reissue claim 4 does not require the active ingredient in the ophthalmically acceptable aqueous pharmaceutical solution to be present in a concentration from 0.1 to 5.0% w/v or for the ophthalmically acceptable aqueous pharmaceutical solution to have a pH of 3.5 to 6.0.

f. Reissue claim 5 is dependent on reissue claim 4 with the added limitation that the disease to be treated by the method in claim 4 is conjunctivitis. Reissue claim 5 differs from original claims 1-3 because reissue claim 5 recites the method of treating conjunctivitis, a utility not claimed in original claims 1-3.

g. Reissue claim 6 is dependent on reissue claim 5 with the added limitation that the disease to be treated by the method in reissue claim 5 is seasonal allergic conjunctivitis. Reissue claim 6 differs from original claims 1-3 because reissue claim 6 recites the method of treating seasonal allergic conjunctivitis, a utility not claimed in original claims 1-3.

h. Reissue claim 7 is dependent on reissue claim 5 with the added limitation that the disease to be treated by the method in reissue claim 5 is allergic conjunctivitis. Reissue claim 7 differs from original claims 1-3 because reissue claim 7 recites the method of treating allergic conjunctivitis, a utility not claimed in original claims 1-3.

I. Reissue claim 8 is dependent on reissue claim 5 with the added limitation that the disease to be treated by the method in reissue claim 5 is vernal conjunctivitis. Reissue claim 8 differs from original claims 1-3 because reissue claim 8 recites the method of treating vernal conjunctivitis, a utility not claimed in original claims 1-3.

j. Reissue claim 9 is a multiple dependent claim dependent on reissue claims 4, 5, 6, 7, or 8 with the added limitation that the active ingredient is nedocromil sodium. Reissue claim 9 differs from original claims 1-3 because it recites the use of nedocromil sodium as the active ingredient in the method of treating a disease selected from the group consisting of conjunctivitis, seasonal allergic conjunctivitis, allergic conjunctivitis, vernal conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, a utility not claimed in original claims 1-3.

k. Reissue claim 10 is an independent claim which recites a method of controlling the symptoms of conjunctivitis comprising administering to the eye of a patient having conjunctivitis an effective amount of nedocromil sodium in an ophthalmically acceptable formulation. Reissue claim 10 differs from original claims 1-3 because reissue claim 10 recites a method of controlling the symptoms of conjunctivitis, a utility not claimed in original claims 1-3. Reissue claim 10 also differs from original claims 1-3 because reissue claim 10 does not contain limitations on the concentration of the active ingredient in the aqueous pharmaceutical solution or the pH of the aqueous pharmaceutical solution. Further, reissue claim 10 recites "administering to the eye an effective amount of nedocromil sodium in an ophthalmically acceptable formulation," whereas original claims 1-3 recite "administering, by inhalation,. . .the nebulized contents of an ampoule of carbon dioxide permeable plastics material filled with a unit dose" of the aqueous pharmaceutical solution.

l. Reissue claim 11 is dependent on reissue claim 10 with the added limitation that the symptoms of the disease to be controlled by the method of reissue claim 10 is vernal conjunctivitis. Reissue claim 11 differs from original claims 1-3 because reissue claim 11 recites the method of controlling the symptoms of vernal conjunctivitis, a utility not claimed in original claims 1-3.

m. Reissue claim 12 is dependent on reissue claim 10 with the added limitation that the symptoms of the disease to be controlled by the method of reissue claim 10 is allergic conjunctivitis. Reissue claim 12 differs from original claims 1-3 because reissue claim 11 recites the method of controlling the symptoms of allergic conjunctivitis, a utility not claimed in original claims 1-3.

n. Reissue claim 13 is dependent on reissue claim 10 with the added limitation that the symptoms of the disease to be controlled by the method of reissue claim 10 is seasonal allergic conjunctivitis. Reissue claim 13 differs from original claims 1-3 because reissue claim 13 recites the method of controlling the symptoms of seasonal allergic conjunctivitis, a utility not claimed in original claims 1-3.

14. I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information, of which I am aware, which is material to the patentability this application as defined in 37 C.F.R. 1.56 and 1.175(a)(7); and at this time bring the following U.S. Patents, Foreign patents and other publications to the attention of the U.S. Patent and Trademark Office:

US PATENTS

U.S. Patent 4,328,341
U.S. Patent 4,419,352
U.S. Patent 4,474,787
U.S. Patent 4,698,345
U.S. Patent 4,760,072
U.S. Patent 4,849,427
U.S. Patent 4,866,072
U.S. Patent 4,868,192

FOREIGN PATENTS

0004722 filed January 1983 - Japan
2022078 filed December 1979 - United Kingdom
2157291A filed April 1985 - United Kingdom

OTHER PUBLICATIONS

Patel, K.R. "Dose-Response Study of Sodium Cromoglycate in Exercise- Induced Asthma," Thorax, vol. 37, pp. 663-666.

Br. J. Clin. Pharmac. vol. 24, Oct. 1987, pp. 493-501, "The Pharmacokinetics of Nedocromil Sodium, a New Drug for the Treatment of Reversible Obstructive Airways Disease, in Human Volunteers and Patients With Reversible Obstructive Airways Disease."

J. Med. Chem. vol. 28, No. 12, 1985, pp. 1832-1842, American Chemical Society, H. Cairns, et al., "New Antiallergic Pyrano(3,2-g) quinoline - 2,8-dicarboxylic Acids with Potential for the Topical Treatment of Asthma."

P.H. List: "Arzneiformenlehre" Chapter Konservierungmittel pp. 369-373, 1976.

P.H. List: "Arzneiformenlehre: Chapter Augenarzneien pp. 400-410, 1976.

R. Voight: "Lehrbuch der pharmazcutischen Technologic", Chapter 27 Augentropfen, pp. 459-467, 1975.

Eur. J. Respir. Dis. (Suppl. 147) 1986, pp. 120-131, R. M. Auty: "The clinical development of a new agent for the treatment of airway inflammation, nedocromil sodium (Tilade)".

J. Allergy Clin. Immunol. vol. 79, No. 1, Feb. 19-25, 1987, p. 186, abstract 247. Schwartz et al. "Efficacy of hedocromil sodium. . . ragweed seasonal allergic rhimitis (SAR)".

J. Allergy Clin. Immuno. vol. 80, No. 2, Aug. 1987, pp. 218-222, Corrado et al. "The effect of nedocromil sodium on nasal provocation with allergan."

J. Allergy Clin. Imunol., vol. 81, No. 3, Mar. 1988, pp. 570-574 Ruhno et al. "Intranasal nedocromil sodium in the treatment of ragweed-allegic rhinitis."

Invest. Ophtalmol. Visual Sci. vol. 29, May 1-6, 1988, p. 229, Stockwell et al. "Dougle blind group comparative trial of 2% nedocromil . . . seasonal allergic conjunctivitis."

Pharmazie, vol. 37, No. 4, 1982, pp. 261-263 Pohloudck-Fabini et al. "Zur Stabilitat der Phenylquecksilbersalzc."

Journal of Pharmaceutical Sciences, vol. 65, No. 4, Apr. 1976, pp. 628-630, Grady et al. "Testing of heat sealing by thermal analysis."

R. Voight, "Lehrbuch der pharmazeutischen Technologic," 5th edition, 1984, pp. 554-557, Verlag Chemie, Weinheim, DE.

The listing above should not be construed as evidencing any belief that all of these references are prior art. In fact, these references are those that are cited on the face of U.S. Patent 5,443,883.

I therefore respectfully request that a Reissue Patent be granted to me for the invention or discovery described and claimed in said letters patent and in the foregoing specification and claims, and I subscribe my name to the foregoing petition, specification, and claims, and declaration and power of attorney.

I declare further that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.

Andrew Clark
436 Valdez Avenue
Half Moon Bay, CA 94019
Citizenship: Great Britain

Date: AUG 18th 1994.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application for Reissue of: Patent No. 5,443,833		§	
Patentees:	ANDREW R. CLARK PAUL WRIGHT JULIA H. RATCLIFFE	§ § §	Attorney Docket No.: 2553.004
Assignee:	Fisons, plc	§	
Issued:	August 22, 1995	§	
For:	PHARMACEUTICAL COMPOSITIONS	§	

REISSUE DECLARATION OF PAUL WRIGHT
UNDER 37 C.F.R. 1.63 AND 1.175(a)

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

As a below-named inventor, I hereby declare:

1. My residence, post office address, and citizenship are as stated below, underneath my name.

2. I verily believe Andrew R. Clark, Paul Wright, and Julia H. Ratcliffe to be the original, first, and joint inventors of the subject matter which is claimed in original Letters Patent No. 5,443,833 granted August 22, 1995, based upon Application Serial No. 08/082,804 filed June 25, 1993 as a continuation of Application Serial No. 07/742,574 filed August 7, 1991, now abandoned, which is a continuation of Application Serial No. 07/410,020 filed September 20, 1989,

now abandoned, which is a continuation of Application Serial No. 07/133,520 filed December 16, 1987, now abandoned, and Andrew R. Clark, Paul Wright, and Julia H. Ratcliffe to be the original, first, and joint inventors of the subject matter of the invention claimed in this application for a reissue patent being filed concurrently herewith.

3. As set forth in my original Declaration for Patent Application, I claim foreign priority benefits under Title 35 United States Code, § 119 of the following foreign applications for patent or inventors certificate and have also identified below any foreign application for patent or inventors certificate having a filing date before that of the application on which priority is claimed:

Great Britain - 86/30767, filed December 23, 1986 - Priority claimed
Great Britain - 86/30769, filed December 23, 1986 - Priority claimed
Great Britain - 86/30904, filed December 24, 1986 - Priority claimed
Great Britain - 87/06684, filed March 20, 1987 - Priority claimed

4. At the time US Application Serial No. 07/133,520 was filed, I was an employee of Fisons, plc, of Ipswich England. In May 1995, I left the employ of Fisons plc. I further recall that Andrew Clark and Julia Ratcliffe left the employ of Fisons plc sometime before that time. I do not have any information concerning the current whereabouts of Julia Ratcliffe. However, upon information and belief, and as evidenced by the Declaration for Patent Application filed with the original application, Julia Ratcliffe is a citizen of Great Britain and she used to reside at Flat 2, 16 Crescent Road, Alverstoke, Gosport Hampshire, England, her last known address. It is also my understanding that Andrew Clark is a citizen of Great Britain. I believe that he currently resides in the United States.

5. I have reviewed and understood the contents of the specification, including the claims, of this reissue application.

6. I do not know and do not believe that said invention was ever known or used in the United States before my invention thereof.

7. I verily believe the original patent to be wholly or partly inoperative or invalid by reason of claiming less than I had a right to claim in the patent because claims for the use of the aqueous pharmaceutical solution of original claims 1-3 in the method of treating ophthalmic conditions and controlling the symptoms of ophthalmic conditions were erroneously canceled. When I filed my original application I intended as the utilities of the claimed aqueous pharmaceutical solution containing as active ingredient, 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof, to include methods of treating a disease or condition selected from the group consisting of conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, which comprises administering to the eye an effective amount of an ophthalmically acceptable aqueous pharmaceutical solution; and methods of controlling the symptoms of conjunctivitis comprising administering to the eye of a patient having conjunctivitis an effective amount of nedocromil sodium in an ophthalmically acceptable formulation. This is illustrated in the specification of the original patent, for example col. 1, lines 34-44. In fact, upon information and belief, claims related to a method of treating ophthalmic conditions and those symptoms, were included throughout much of the prosecution of the above referenced applications. Original claims 1-3, the only claims in this patent, do not claim these utilities. I do not have personal knowledge why the aspect of the claims related to the method of treating ophthalmic conditions was canceled. Further I was not consulted when this aspect of the claims was canceled.

8. Upon information and belief, this error arose because the Fisons attorney in charge of handling the prosecution of my application failed to continue prosecution of claims directed at methods of treating ophthalmic diseases and conditions after the examiner had allowed claims directed at treating reversible obstructive airways disease. Upon information and belief, in the original application, and during the prosecution of Application Serial No. 08/082,804, claims reciting methods of treating various types of conditions, including ophthalmic conditions were submitted. Upon information and belief, the Examiner's remarks in the Final Office Action of Application Serial No. 08/082,804 were directed to the formulation of the aqueous pharmaceutical solution claimed in the invention in the treatment of reversible obstructive airways disease. However, upon information and belief, all of the pending claims in the application were canceled in an Amendment after final rejection filed February 13, 1995, including those for methods of treating and controlling the symptoms of ophthalmic conditions, and three new claims unnecessarily limited to methods of treating reversible obstructive airways disease were submitted. These three new claims issued as claims 1-3 in U.S. Patent No. 5,443,833 on August 22, 1995.

9. Upon information and belief, this error occurred due to a failure of the Fisons attorneys to continue prosecution of claims for methods of treating and controlling symptoms of ophthalmic conditions. At the time the error occurred, I was not involved in decisions relating to the prosecution of the application and therefore, all actions relating to the prosecution were made by the Fisons' attorney. Upon information and belief, the failure to continue prosecution of claims directed at a method for treating ophthalmic conditions may have been the result of internal turmoil within Fisons. During 1995, Fisons was acquired by Rhone-Poulenc Rorer, Inc. A number of Fisons employees left the company in this time frame. Upon information and belief, neither Julia

Ratcliffe nor Andrew Clark were involved in the decision to not continue the prosecution of the claims for methods of treating and controlling symptoms of ophthalmic conditions. I am informed that the declaration of Alison Blakey is being submitted to more fully explain the error.

10. This error that rendered this patent wholly or partly inoperative arose entirely from inadvertence, accident, and mistake, and without any fraudulent and/or deceptive intent on my part, or, on my best information and belief, without any fraudulent and/or deceptive intent on the part of Andrew Clark, Julia Ratcliffe or anyone else associated with me.

11. As a result of the Fison's attorneys' erroneous conclusion or decision, the patent is wholly or partly inoperative or invalid by reason of claiming less than I had a right to claim in the patent because original claims 1-3 do not recite the use of the aqueous pharmaceutical solution of original claims 1-3 for use in methods of treating ophthalmic conditions and controlling the symptoms of ophthalmic conditions.

12. Upon information and belief this error was discovered in 1997, during license negotiations for the use of the aqueous pharmaceutical solution claimed in original claims 1-3 for methods of treating ophthalmic diseases and controlling the symptoms of ophthalmic conditions. Upon information and belief, a review of the specification of this patent by the potential licensee revealed support for claims for methods of treating and controlling the symptoms of ophthalmic conditions. Upon information and belief, the potential licensee then reviewed the file history and the prior art cited and relied upon by the Examiner during the prosecution of U.S. Patent No. 5,443,833, and concluded that the claims for methods of treating and controlling symptoms of ophthalmic conditions were patentable. Of course this is consistent with my belief that the subject matter was new and therefore patentable. In fact, as evidence that an error did in fact occur, upon

information and belief, all relevant prior art was cited to the European Patent Office and successfully overcome to establish patentability of claims for methods of treating reversible obstructive airways disease, as well as for methods of treating and controlling the symptoms of ophthalmic conditions.

13. The error of canceling claims which recite the use of the aqueous pharmaceutical solution containing as active ingredient, 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof, as claimed in original claims 1-3, which included methods of treating and controlling the symptoms of ophthalmic conditions is remedied in this reissue application because reissue claims 4-13 recite the use of the aqueous pharmaceutical solution of original claims 1-3 for use in the methods of treating and controlling the symptoms of ophthalmic conditions. Therefore, there is a difference in the scope of the claims 1-3 of U.S. 5,443,833 and the reissue claims. The following identifies all of the reissue claims presently in this application and the differences, if any, between the reissue claims and original claims 1-3:

a. Reissue claims 1-3 are identical to original claims 1-3 issued in this patent.

b. Reissue claim 1 recites the method of treating reversible obstructive airways disease comprising administering, by inhalation, to a patent suffering from, or susceptible to, such a condition the nebulized contents of an ampoule of carbon dioxide permeable plastics material filled with a unit does of an aqueous pharmaceutical solution containing, as active ingredient, from 0.1 to 5% w/v of 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof, the solution having a pH of 3.5 to 6.0. Reissue claim 1 is identical to original claim 1.

c. Reissue claim 2 is dependent on reissue claim 1 with the further limitation that the concentration of the active ingredients in the solution is from 0.1 to 1.0% w/v. Reissue claim 2 is identical to original claim 2.

d. Reissue claim 3 is dependent on reissue claim 1 with the added limitation that the active ingredient is nedocromil sodium. Reissue claim 3 is identical to original claim 3.

e. Reissue claim 4 is an independent claim which recites the method of treatment for a disease selected from the group consisting of conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, which comprises administering to the eye an effective amount of an ophthalmically acceptable aqueous pharmaceutical solution containing an active ingredient 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof. Reissue claim 4 differs from original claims 1-3 because reissue claim 4 recites the use of an ophthalmically acceptable aqueous solution of pharmaceutical solution containing an active ingredient of 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof in the method of treating a disease selected from the group consisting of conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, a utility not claimed in original claims 1-3. Reissue claim 4 also differs from original claims 1-3 because reissue claim 4 recites administering to the eye an effective amount of an ophthalmically acceptable aqueous pharmaceutical solution. Reissue claim 4 does not recite administering the pharmaceutical solution by inhalation, the nebulized contents of an ampoule of carbon dioxide permeable plastics material filled with a unit dose of the aqueous pharmaceutical solution. Further, reissue claim 4 differs from original claims 1-3 because reissue claim 4 does not require the active ingredient in the ophthalmically acceptable aqueous pharmaceutical solution to

be present in a concentration from 0.1 to 5.0% w/v or for the ophthalmically acceptable aqueous pharmaceutical solution to have a pH of 3.5 to 6.0.

f. Reissue claim 5 is dependent on reissue claim 4 with the added limitation that the disease to be treated by the method in claim 4 is conjunctivitis. Reissue claim 5 differs from original claims 1-3 because reissue claim 5 recites the method of treating conjunctivitis, a utility not claimed in original claims 1-3.

g. Reissue claim 6 is dependent on reissue claim 5 with the added limitation that the disease to be treated by the method in reissue claim 5 is seasonal allergic conjunctivitis. Reissue claim 6 differs from original claims 1-3 because reissue claim 6 recites the method of treating seasonal allergic conjunctivitis, a utility not claimed in original claims 1-3.

h. Reissue claim 7 is dependent on reissue claim 5 with the added limitation that the disease to be treated by the method in reissue claim 5 is allergic conjunctivitis. Reissue claim 7 differs from original claims 1-3 because reissue claim 7 recites the method of treating allergic conjunctivitis, a utility not claimed in original claims 1-3.

I. Reissue claim 8 is dependent on reissue claim 5 with the added limitation that the disease to be treated by the method in reissue claim 5 is vernal conjunctivitis. Reissue claim 8 differs from original claims 1-3 because reissue claim 8 recites the method of treating vernal conjunctivitis, a utility not claimed in original claims 1-3.

j. Reissue claim 9 is a multiple dependent claim dependent on reissue claims 4, 5, 6, 7, or 8 with the added limitation that the active ingredient is nedocromil sodium. Reissue claim 9 differs from original claims 1-3 because it recites the use of nedocromil sodium as the active ingredient in the method of treating a disease selected from the group consisting of conjunctivitis,

seasonal allergic conjunctivitis, allergic conjunctivitis, vernal conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, a utility not claimed in original claims 1-3.

k. Reissue claim 10 is an independent claim which recites a method of controlling the symptoms of conjunctivitis comprising administering to the eye of a patient having conjunctivitis an effective amount of nedocromil sodium in an ophthalmically acceptable formulation. Reissue claim 10 differs from original claims 1-3 because reissue claim 10 recites a method of controlling the symptoms of conjunctivitis, a utility not claimed in original claims 1-3. Reissue claim 10 also differs from original claims 1-3 because reissue claim 10 does not contain limitations on the concentration of the active ingredient in the aqueous pharmaceutical solution or the pH of the aqueous pharmaceutical solution. Further, reissue claim 10 recites "administering to the eye an effective amount of nedocromil sodium in an ophthalmically acceptable formulation," whereas original claims 1-3 recite "administering, by inhalation,. . .the nebulized contents of an ampoule of carbon dioxide permeable plastics material filled with a unit dose" of the aqueous pharmaceutical solution.

l. Reissue claim 11 is dependent on reissue claim 10 with the added limitation that the symptoms of the disease to be controlled by the method of reissue claim 10 is vernal conjunctivitis. Reissue claim 11 differs from original claims 1-3 because reissue claim 11 recites the method of controlling the symptoms of vernal conjunctivitis, a utility not claimed in original claims 1-3.

m. Reissue claim 12 is dependent on reissue claim 10 with the added limitation that the symptoms of the disease to be controlled by the method of reissue claim 10 is allergic conjunctivitis. Reissue claim 12 differs from original claims 1-3 because reissue claim 11 recites

the method of controlling the symptoms of allergic conjunctivitis, a utility not claimed in original claims 1-3.

n. Reissue claim 13 is dependent on reissue claim 10 with the added limitation that the symptoms of the disease to be controlled by the method of reissue claim 10 is seasonal allergic conjunctivitis. Reissue claim 13 differs from original claims 1-3 because reissue claim 13 recites the method of controlling the symptoms of seasonal allergic conjunctivitis, a utility not claimed in original claims 1-3.

14. I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information, of which I am aware, which is material to the patentability this application as defined in 37 C.F.R. 1.56 and 1.175(a)(7); and at this time bring the following U.S. Patents, Foreign patents and other publications to the attention of the U.S. Patent and Trademark Office:

US PATENTS

U.S. Patent 4,328,341
U.S. Patent 4,419,352
U.S. Patent 4,474,787
U.S. Patent 4,698,345
U.S. Patent 4,760,072
U.S. Patent 4,849,427
U.S. Patent 4,866,072
U.S. Patent 4,868,192

FOREIGN PATENTS

0004722 filed January 1983 - Japan
2022078 filed December 1979 - United Kingdom
2157291A filed April 1985 - United Kingdom

OTHER PUBLICATIONS

Patel, K.R. "Dose-Response Study of Sodium Cromoglycate in Exercise- Induced Asthma," Thorax, vol. 37, pp. 663-666.

Br. J. Clin. Pharmac. vol. 24, Oct. 1987, pp. 493-501, "The Pharmacokinetics of Nedocromil Sodium, a New Drug for the Treatment of Reversible Obstructive Airways Disease, in Human Volunteers and Patients With Reversible Obstructive Airways Disease."

J. Med. Chem. vol. 28, No. 12, 1985, pp. 1832-1842, American Chemical Society, H. Cairns, et al., "New Antiallergic Pyrano(3,2-g) quinoline - 2,8-dicarboxylic Acids with Potential for the Topical Treatment of Asthma."

P.H. List: "Arzneiformenlehre" Chapter Konservierungmittel pp. 369-373, 1976.

P.H. List: "Arzneiformenlehre: Chapter Augenarzneien pp. 400-410, 1976.

R. Voight: "Lehrbuch der pharmazcutischen Technologic", Chapter 27 Augentropfen, pp. 459-467, 1975.

Eur. J. Respir. Dis. (Suppl. 147) 1986, pp. 120-131, R. M. Auty: "The clinical development of a new agent for the treatment of airway inflammation, nedocromil sodium (Tilade)".

J. Allergy Clin. Immunol. vol. 79, No. 1, Feb. 19-25, 1987, p. 186, abstract 247. Schwartz et al. "Efficacy of hedocromil sodium. . . ragweed seasonal allergic rhimitis (SAR)".

J. Allergy Clin. Immuno. vol. 80, No. 2, Aug. 1987, pp. 218-222, Corrado et al. "The effect of nedocromil sodium on nasal provocation with Allergan."

J. Allergy Clin. Imunol., vol. 81, No. 3, Mar. 1988, pp. 570-574 Ruhno et al. "Intranasal nedocromil sodium in the treatment of ragweed-allegic rhinitis."

Invest. Ophtalmol. Visual Sci. vol. 29, May 1-6, 1988, p. 229, Stockwell et al. "Dougle blind group comparative trial of 2% nedocromil . . . seasonal allergic conjunctivitis."

Pharmazie, vol. 37, No. 4, 1982, pp. 261-263 Pohloudck-Fabini et al. "Zur Stabilitat der Phenylquecksilbersalzc."

Journal of Pharmaceutical Sciences, vol. 65, No. 4, Apr. 1976, pp. 628-630, Grady et al. "Testing of heat sealing by thermal analysis."

R. Voight, "Lehrbuch der pharmazeutischen Technologic," 5th edition, 1984, pp. 554-557, Verlag Chemie, Weinheim, DE.

The listing above should not be construed as evidencing any belief that all of these references are prior art. In fact, these references are those that are cited on the face of U.S. Patent 5,443,883.

I therefore respectfully request that a Reissue Patent be granted to me for the invention or discovery described and claimed in said letters patent and in the foregoing specification and claims, and I subscribe my name to the foregoing petition, specification, and claims, and declaration and power of attorney.

I declare further that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.

I have no access to written records, and hence my agreement is from memory

Paul Wright
9 Thornhill Close
Bramcote, England
Citizenship: Great Britain

Date: 26/11/97

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application for Reissue of:		§	
Patent No. 5,443,833		§	
		§	
Patentees:	ANDREW R. CLARK	§	
	PAUL WRIGHT	§	
	JULIA H. RATCLIFFE	§	Attorney Docket No.: 2553.004
		§	
Assignee:	Fisons, plc	§	
		§	
Issued:	August 22, 1995	§	
		§	
For:	PHARMACEUTICAL COMPOSITIONS	§	

REISSUE DECLARATION OF JULIA RATCLIFFE UNDER 37 C.F.R. 1.63 AND 1.175(a)

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

As a below-named inventor, I hereby declare:

1. My residence, post office address, and citizenship are as stated below, underneath my name.

2. I verily believe Andrew R. Clark, Paul Wright, and Julia H. Ratcliffe to be the original, first, and joint inventors of the subject matter which is claimed in original Letters Patent No. 5,443,833 granted August 22, 1995, based upon Application Serial No. 08/082,804 filed June 25, 1993 as a continuation of Application Serial No. 07/742,574 filed August 7, 1991, now abandoned, which is a continuation of Application Serial No. 07/410,020 filed September 20, 1989,

now abandoned, which is a continuation of Application Serial No. 07/133,520 filed December 16, 1987, now abandoned, and Andrew R. Clark, Paul Wright, and Julia H. Ratcliffe to be the original, first, and joint inventors of the subject matter of the invention claimed in the application for a reissue patent filed August 21, 1997.

3. As set forth in my original Declaration for Patent Application, I claim foreign priority benefits under Title 35 United States Code, § 119 of the following foreign applications for patent or inventors certificate and have also identified below any foreign application for patent or inventors certificate having a filing date before that of the application on which priority is claimed:

Great Britain - 86/30767, filed December 23, 1986 - Priority claimed
Great Britain - 86/30769, filed December 23, 1986 - Priority claimed
Great Britain - 86/30904, filed December 24, 1986 - Priority claimed
Great Britain - 87/06684, filed March 20, 1987 - Priority claimed

4. At the time US Application Serial No. 07/133,520 was filed, I was an employee of Fisons, plc, of Ipswich England. In 1986 or 1987, I left the employ of Fisons plc.

5. I have reviewed and understood the contents of the specification, including the claims, of this reissue application.

6. I do not know and do not believe that said invention was ever known or used in the United States before my invention thereof.

7. I verily believe the original patent to be wholly or partly inoperative or invalid by reason of claiming less than I had a right to claim in the patent because claims for the use of the aqueous pharmaceutical solution of original claims 1-3 in the method of treating ophthalmic conditions and controlling the symptoms of ophthalmic conditions were erroneously canceled. When I filed my original application the intended utilities of the claimed aqueous pharmaceutical

solution containing as active ingredient, 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof, included methods of treating a disease or condition selected from the group consisting of conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, which comprises administering to the eye an effective amount of an ophthalmically acceptable aqueous pharmaceutical solution; and methods of controlling the symptoms of conjunctivitis comprising administering to the eye of a patient having conjunctivitis an effective amount of nedocromil sodium in an ophthalmically acceptable formulation. This is illustrated in the body of the original patent, for example col. 1, lines 34-44. In fact, upon information and belief, claims related to a method of treating ophthalmic conditions and those symptoms, were included throughout much of the prosecution of the above referenced applications. Original claims 1-3, the only claims in this patent, do not claim these utilities. I do not have personal knowledge why the aspect of the claims related to the method of treating ophthalmic conditions was canceled. Further I was not consulted when this aspect of the claims was canceled. In fact, I do not recall having any substantive involvement in the prosecution of the applications leading to the issuance of the original patent after I left the employ of Fisons plc.

8. Upon information and belief, this error arose because the Fisons attorney in charge of handling the prosecution of my application failed to continue prosecution of claims directed at methods of treating ophthalmic diseases and conditions after the examiner had allowed claims directed at treating reversible obstructive airways disease. Upon information and belief, in the original application, and during the prosecution of Application Serial No. 08/082,804, claims reciting methods of treating various types of conditions, including ophthalmic conditions were submitted. Upon information and belief, the Examiner's remarks in the Final Office Action of Application

Serial No. 08/082,804 were directed to the formulation of the aqueous pharmaceutical solution claimed in the invention in the treatment of reversible obstructive airways disease. However, upon information and belief, all of the pending claims in the application were canceled in an Amendment after the final rejection filed February 13, 1995, including those for methods of treating and controlling the symptoms of ophthalmic conditions, and three new claims unnecessarily limited to methods of treating reversible obstructive airways disease were submitted. These three new claims issued as claims 1-3 in U.S. Patent No. 5,443,833 on August 22, 1995.

9. Upon information and belief, this error occurred due to a failure of the Fisons attorneys to continue prosecution of claims for methods of treating and controlling symptoms of ophthalmic conditions. At the time the error occurred, I was not involved in decisions relating to the prosecution of the application and therefore, all actions relating to the prosecution was made by the Fisons' attorneys. Upon information and belief, the failure to continue prosecution of claims directed at a method for treating ophthalmic conditions may have been the result of internal turmoil within Fisons plc. Upon information and belief, during 1995, Fisons plc was acquired by Rhone-Poulenc Rorer, Inc. and a number of Fisons employees left the company in this time frame. As explained above, I left the employ of Fisons before the amendment was made. I am informed that the declaration of Alison Blakey was submitted to more fully explain the error.

10. This error that rendered this patent wholly or partly inoperative arose entirely from inadvertence, accident, and mistake, and without any fraudulent and/or deceptive intent on my part, or, on my best information and belief, without any fraudulent and/or deceptive intent on the part of Paul Wright, Andrew Clark or anyone else associated with me.

11. As a result of the Fison's attorneys' erroneous conclusion or decision, the patent is wholly or partly inoperative or invalid by reason of claiming less than I had a right to claim in the patent because original claims 1-3 do not recite the use of the aqueous pharmaceutical solution of original claims 1-3 for use in methods of treating ophthalmic conditions and controlling the symptoms of ophthalmic conditions.

12. Upon information and belief this error was discovered in 1997, during license negotiations for the use of the aqueous pharmaceutical solution claimed in original claims 1-3 for methods of treating ophthalmic diseases and controlling the symptoms of ophthalmic conditions. Upon information and belief, a review of the specification of this patent by the potential licensee revealed support for claims for methods of treating and controlling the symptoms of ophthalmic conditions. Upon information and belief, the potential licensee then reviewed the file history and the prior art cited and relied upon by the Examiner during the prosecution of U.S. Patent No. 5,443,833, and concluded that the claims for methods of treating and controlling symptoms of ophthalmic conditions were patentable. Of course this is consistent with my belief that the subject matter was new and therefore patentable. In fact, as evidence that an error did in fact occur, upon information and belief, all relevant prior art was cited to the European Patent Office and successfully overcome to establish patentability of claims for methods of treating reversible obstructive airways disease, as well as for methods of treating and controlling the symptoms of ophthalmic conditions.

13. The error of canceling claims which recite the use of the aqueous pharmaceutical solution containing as active ingredient, 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof, as claimed in original claims 1-3, which included methods of treating and controlling the symptoms

of ophthalmic conditions is remedied in this reissue application because reissue claims 4-13 recite the use of the aqueous pharmaceutical solution of original claims 1-3 for use in the methods of treating and controlling the symptoms of ophthalmic conditions. Therefore, there is a difference in the scope of the claims 1-3 of U.S. 5,443,833 and the reissue claims. The following identifies all of the reissue claims presently in this application and the differences, if any, between the reissue claims and original claims 1-3:

a. Reissue claims 1-3 are identical to original claims 1-3 issued in this patent.

b. Reissue claim 1 recites the method of treating reversible obstructive airways disease comprising administering, by inhalation, to a patent suffering from, or susceptible to, such a condition the nebulized contents of an ampoule of carbon dioxide permeable plastics material filled with a unit dose of an aqueous pharmaceutical solution containing, as active ingredient, from 0.1 to 5% w/v of 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof, the solution having a pH of 3.5 to 6.0. Reissue claim 1 is identical to original claim 1.

c. Reissue claim 2 is dependent on reissue claim 1 with the further limitation that the concentration of the active ingredients in the solution is from 0.1 to 1.0% w/v. Reissue claim 2 is identical to original claim 2.

d. Reissue claim 3 is dependent on reissue claim 1 with the added limitation that the active ingredient is nedocromil sodium. Reissue claim 3 is identical to original claim 3.

e. Reissue claim 4 is an independent claim which recites the method of treatment for a disease selected from the group consisting of conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, which comprises administering to the eye an effective amount of an ophthalmically

acceptable aqueous pharmaceutical solution containing an active ingredient 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof. Reissue claim 4 differs from original claims 1-3 because reissue claim 4 recites the use of an ophthalmically acceptable aqueous solution of pharmaceutical solution containing an active ingredient of 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-4H-pyrano(3,2g)quinoline-2, 8 dicarboxylic acid, or a pharmaceutically acceptable salt thereof in the method of treating a disease selected from the group consisting of conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, a utility not claimed in original claims 1-3. Reissue claim 4 also differs from original claims 1-3 because reissue claim 4 recites administering to the eye an effective amount of an ophthalmically acceptable aqueous pharmaceutical solution. Reissue claim 4 does not recite administering the pharmaceutical solution by inhalation, the nebulized contents of an ampoule of carbon dioxide permeable plastics material filled with a unit dose of the aqueous pharmaceutical solution. Further, reissue claim 4 differs from original claims 1-3 because reissue claim 4 does not require the active ingredient in the ophthalmically acceptable aqueous pharmaceutical solution to be present in a concentration from 0.1 to 5.0% w/v or for the ophthalmically acceptable aqueous pharmaceutical solution to have a pH of 3.5 to 6.0.

f. Reissue claim 5 is dependent on reissue claim 4 with the added limitation that the disease to be treated by the method in claim 4 is conjunctivitis. Reissue claim 5 differs from original claims 1-3 because reissue claim 5 recites the method of treating conjunctivitis, a utility not claimed in original claims 1-3.

g. Reissue claim 6 is dependent on reissue claim 5 with the added limitation that the disease to be treated by the method in reissue claim 5 is seasonal allergic conjunctivitis. Reissue

claim 6 differs from original claims 1-3 because reissue claim 6 recites the method of treating seasonal allergic conjunctivitis, a utility not claimed in original claims 1-3.

h. Reissue claim 7 is dependent on reissue claim 5 with the added limitation that the disease to be treated by the method in reissue claim 5 is allergic conjunctivitis. Reissue claim 7 differs from original claims 1-3 because reissue claim 7 recites the method of treating allergic conjunctivitis, a utility not claimed in original claims 1-3.

I. Reissue claim 8 is dependent on reissue claim 5 with the added limitation that the disease to be treated by the method in reissue claim 5 is vernal conjunctivitis. Reissue claim 8 differs from original claims 1-3 because reissue claim 8 recites the method of treating vernal conjunctivitis, a utility not claimed in original claims 1-3.

j. Reissue claim 9 is a multiple dependent claim dependent on reissue claims 4, 5, 6, 7, or 8 with the added limitation that the active ingredient is nedocromil sodium. Reissue claim 9 differs from original claims 1-3 because it recites the use of nedocromil sodium as the active ingredient in the method of treating a disease selected from the group consisting of conjunctivitis, seasonal allergic conjunctivitis, allergic conjunctivitis, vernal conjunctivitis, keratitis, "allergic eyes," and anterior uveitis, a utility not claimed in original claims 1-3.

k. Reissue claim 10 is an independent claim which recites a method of controlling the symptoms of conjunctivitis comprising administering to the eye of a patient having conjunctivitis an effective amount of nedocromil sodium in an ophthalmically acceptable formulation. Reissue claim 10 differs from original claims 1-3 because reissue claim 10 recites a method of controlling the symptoms of conjunctivitis, a utility not claimed in original claims 1-3. Reissue claim 10 also differs from original claims 1-3 because reissue claim 10 does not contain

limitations on the concentration of the active ingredient in the aqueous pharmaceutical solution or the pH of the aqueous pharmaceutical solution. Further, reissue claim 10 recites "administering to the eye an effective amount of nedocromil sodium in an ophthalmically acceptable formulation," whereas original claims 1-3 recite "administering, by inhalation,. . .the nebulized contents of an ampoule of carbon dioxide permeable plastics material filled with a unit dose" of the aqueous pharmaceutical solution.

l. Reissue claim 11 is dependent on reissue claim 10 with the added limitation that the symptoms of the disease to be controlled by the method of reissue claim 10 is vernal conjunctivitis. Reissue claim 11 differs from original claims 1-3 because reissue claim 11 recites the method of controlling the symptoms of vernal conjunctivitis, a utility not claimed in original claims 1-3.

m. Reissue claim 12 is dependent on reissue claim 10 with the added limitation that the symptoms of the disease to be controlled by the method of reissue claim 10 is allergic conjunctivitis. Reissue claim 12 differs from original claims 1-3 because reissue claim 11 recites the method of controlling the symptoms of allergic conjunctivitis, a utility not claimed in original claims 1-3.

n. Reissue claim 13 is dependent on reissue claim 10 with the added limitation that the symptoms of the disease to be controlled by the method of reissue claim 10 is seasonal allergic conjunctivitis. Reissue claim 13 differs from original claims 1-3 because reissue claim 13 recites the method of controlling the symptoms of seasonal allergic conjunctivitis, a utility not claimed in original claims 1-3.

14. I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information, of which I am aware, which is material to the patentability this application as defined in 37 C.F.R. 1.56 and 1.175(a)(7); and at this time bring the following U.S. Patents, Foreign patents and other publications to the attention of the U.S. Patent and Trademark Office:

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U.S. Patent 4,866,072
U.S. Patent 4,868,192

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OTHER PUBLICATIONS

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Journal of Pharmaceutical Sciences, vol. 65, No. 4, Apr. 1976, pp. 628-630, Grady et al. "Testing of heat sealing by thermal analysis."

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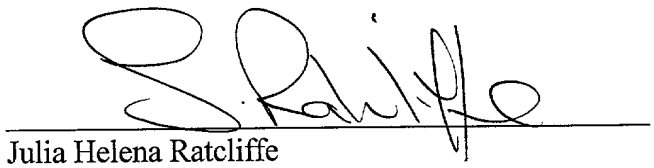
The listing above should not be construed as evidencing any belief that all of these references are prior art. In fact, these references are those that are cited on the face of U.S. Patent 5,443,883.

I therefore respectfully request that a Reissue Patent be granted to me for the invention or discovery described and claimed in said letters patent and in the foregoing specification and claims, and I subscribe my name to the foregoing petition, specification, and claims, and declaration and power of attorney.

I declare further that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements

were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.



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Date: 4/11/97

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application for Reissue of: Patent No. 5,443,833		§	
Patentee:	ANDREW R. CLARK PAUL WRIGHT JULIA H. RATCLIFFE	§ § §	Attorney Docket No.: 2553.004
Issued:	August 22, 1995	§	
For:	PHARMACEUTICAL COMPOSITIONS	§ §	

POWER OF ATTORNEY

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

The undersigned, Assignee of the entire interest in the above-mentioned Letters Patent and the above-identified reissue application, hereby revoke any previous powers of attorney and appoint Edward W. Goldstein, Reg. No. 22,945, and Ben D. Tobor, Reg. No. 27,760, with full power of substitution and revocation, to prosecute this reissue application, to make alterations and amendments therein, to transact all business in the Patent and Trademark Office in connection therewith, and to receive the Letters Patent.

Please direct all communications as follows:

Edward W. Goldstein (EWG/2553.004)
Tobor & Goldstein, L.L.P.
1360 Post Oak Blvd., Suite 2300
Houston, Texas 77056
Telephone: (713) 877-1515
Facsimile: (713) 877-1145

Assignee, Fisons plc

Date: August 15, 1997

By: Timothy G. Rothwell

Name: Timothy G. Rothwell

Title: Director

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application for Reissue of: Patent No. 5,443,833		§	
Patentee:	ANDREW R. CLARK PAUL WRIGHT JULIA H. RATCLIFFE	§ § §	Attorney Docket No.: 2553.004
Issued:	August 22, 1995	§	
For:	PHARMACEUTICAL COMPOSITIONS	§ §	

ASSENT OF ASSIGNEE TO REISSUE

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

The undersigned, Assignee of the entire interest in the above-mentioned Letters Patent, assents to the accompanying reissue application.

Fisons plc

By: _____
Name: Timothy G. Rothwell
Title: Director

Date: August 15, 1997

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application for Reissue of: Patent No. 5,443,833		§	
Patentee:	ANDREW R. CLARK PAUL WRIGHT JULIA H. RATCLIFFE	§ § §	Attorney Docket No.: 2553.004
Issued:	August 22, 1995	§	
For:	PHARMACEUTICAL COMPOSITIONS	§ §	

OFFER TO SURRENDER

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In accordance with the provisions of 37 C.F.R. § 1.171 and 37 C.F.R.§ 1.178, the undersigned assignee of the entire interest of Letters Patent for Pharmaceutical Compositions, U.S. Patent No. 5,443,833, issued on August 22, 1995, hereby offers to surrender the original Letters Patent.

A request for Order for Title Report as required for such application is filed concurrently herewith.

Fisons plc

By: Timothy G. Rothwell
Name: Timothy G. Rothwell
Title: Director

Date: August 15, 1997